REMARKS

Support for the claims can be found through the specification, e.g., Claims 124 and 174, Page 6, line 24-Page 9, line 22, Example 1 on Page 28, lines 13-29, Page 42, line 16-Page 43, line 35; Claims 182 and 184, Page 5, lines 30-32; Claims 183 and 185, Page 4, lines 30-34 and Page 6, lines 7-9; Claim 186, Page 46, lines 16-25; Claims 187 and 188, Page 42, line 16; Claims 189-192, Page 47, lines 27-29, Example 12, and Page 3, line 11-Page 4, line 34.

The amendment filed March 4, 2004 was denied entry. The amendment herein is submitted in place of the un-entered March 4, 2004 amendment.

It is believed that following amendments place the application in condition for allowance, or at the very least, simplify the issues for appeal. For example, in an earlier teleconference with the examiner, the examiner had pointed out that the previously filed claims did not expressly distinguish over the prior art. As discussed in more detail below, it is believed that this aspect has now been adequately addressed.

Rejection under §112, first paragraph

The claims are rejected on Pages 3-5 of the Office action as lacking a written description. See, Office action (Date mailed, September 15, 2003), Paragraph No. 3.

It is stated in the Office action (Page 4, lines 1-2) that "Applicants have not identified a 'function' which would allow for determining members of the genus." Although applicants do not necessarily agree that such information is necessary to meet the requirements of §112, first paragraph, from the discussion below, it is evident that even by this standard, the claims are fully in conformance with the statute.

As described in the specification, Neisseria meningitidis is a pathogenic organism which is a major cause of death and morbidity throughout the world. It is one of the principal causes of bacterial meningitis in the United States, accounting for approximately 20% of all cases. See, e.g., Specification, Page 1, line 19-Page 2, line 5. There remains a great need for protective vaccines and diagnostic assays. See, e.g., Specification, Page 4, line 20-Page 5, line 21.

The claimed surface proteins have several specific, substantial, and credible functions. For example, they are highly specific for Neisseria pathogenic bacteria, and

therefore valuable as diagnostic tools, e.g., to determine the presence or absence of infection. See, e.g., Specification, Page 22, line 32-Page 23, line 4. In addition, the proteins can be used to elicit bacteriolytic activity, and, as a result, are useful to provide protection against Neisseria infection. See, e.g., Specification, Page 16, lines 3-9. These concepts are described throughout the application. They are inherent to the polypeptides, and it is unnecessary that these functions be recited in the claims.

The inventors have discovered that the claimed surface polypeptides are uniquely present in Neisseria pathogenic bacteria. The results are described in Example 2 of the specification. See, especially Page 37, lines 11-29. Table 2 (Page 48) shows that the polypeptides are specific for Neisseria, but not present, or not reactive with antibodies to them, in 31 other species and strains tested. (See, also, Table 1, Page 39; Page 37, line 11-29.) These results clearly establish the specificity of the polypeptides for Neisseria, and the value of antibodies specific to them for diagnostic testing. See, e.g., Specification, Page 5, lines 1-21. Example 8 (Page 55, line 21) shows that the ability to generate specific antibodies is not restricted to mice, but the polypeptides can also elicit a specific immune response in rabbits and monkeys.

In the Office action (Page 3, fourth paragraph), it was stated that antigenicity is a function "shared by every protein in the known universe." As explained above, the Neisseria surface protein has properties very specific to it: (1) present on the cell surface of Neisseria and therefore a unique identifier for it, (2) capable of eliciting antibodies that are specific to said polypeptide, and/or (3) capable of eliciting bacteriolytic antibodies against Neisseria. See, e.g., Claims 182-185. These functions are *specific* to the claimed polypeptides, and are sufficient to meet the statutory requirements. Indeed, there are legions of patents that have been granted on vaccines comprising polypeptides.

The polypeptides are also useful in prophylactic and therapeutic applications. See, Specification, Page 21, lines 14-33. Example 5, beginning on Page 49, shows that antibodies to the claimed polypeptides in both *in vitro* and *in vivo* models possessed bacteriolytic activity against Neisseria, protecting animals against a lethal challenge with the bacteria. Moreover, purified polypeptide, when injected into mice, also provided significant protection after challenge with Neisseria meningitidis. These results are described in Example 6, beginning on Page 51. Thus, the claims polypeptide alone, or

when formulated with other polypeptides, including with other Neisseria polypeptides, can be used to manufacture effective prophylactic and/or therapeutic compositions.

The Patent Office's published *Written Description Guidelines* were intended to provide guidance to the public and the examining groups on what elements are considered necessary by the agency to meet the written description requirements. Example 9 provides this guidance for hybridization-type claims. While applicants may not agree with the agency's interpretation, nonetheless the pending claims meet these requirements as outlined by the *Guidelines*.

The PTO's example provides a claim to sequences that hybridize to a recited sequence, and which encode proteins with a particular activity. ("An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.") The elements set forth as being adequate to fulfill the written description requirements included: (1) the protein's dopaminergic activity; (2) "a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus"; and (3) hybridization conditions that "yield structurally similar DNAs."

The pending claims meet these criteria. The specificity, bacteriolytic, and protective functions/properties of polypeptides were described in detail above. Clearly, this first element is met. Secondly, not one, but four different species within the scope of the claimed genus are disclosed. See, Figs. 11 and 12. Finally, DNA hybridization under stringent conditions identified structurally related DNA. The data for this is summarized in Table 2 on Page 48, and was confirmed by the sequence analysis provided in Example 7. ("In conclusion, the DNA hybridization assay clearly indicated that the gene coding for Neisseria meningitidis 22 kDa surface protein is highly conserved among the pathogenic Neisseria." Page 48, line 26-Page 49, line 2.) Figs. 11 and 12 show the extremely high degree of structural identity between four different polypeptides and polynucleotides. (For example, the sequence homology between 608B and Z4063 is 99% for DNA, and 98% at the amino acid level; between 608B and MCH88 is 96% for DNA, and 95% at the amino acid level; between 608B and gonoB2 is 97% for DNA, and 94% at the amino acid level.) Taken together, it is evidence that the specification clearly

provides the information set forth by the U.S. Patent Office as needed to meet the statutory requirements for a hybridization claim.

Claim 174 recites "An isolated polypeptide from the surface of Neisseria bacteria which (i) is resistant to proteinase K, (ii) has an apparent molecular weight of 22 kDa, and (iii) is stained by Coomassie blue, wherein said polypeptide is antigenic." According to the M.P.E.P. 2163: "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406." The specification provides at least four examples of polypeptides that fall within the claimed genus, and discloses a consensus sequence (Fig. 12) that reveals the "common attributes or features of the elements possessed by members of the genus." *Written Description Guidelines*, Page 39, last sentence. This claim is also in conformance with the statutory requirements.

Claims 133-137 and 170-173 are also rejected under §112, first paragraph, because the specification allegedly "does not provide enablement for pharmaceutical/vaccine compositions comprising a polypeptide which hybridizes under stringent conditions a DNA sequence encoding a Neisseria surface protein." Office action, Page 5, No. 4.

As argued by applicant in the previous response, the examiner has not satisfied "the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." M.P.E.P. §2164.04. Only boilerplate objections have been provided. In contrast, the specification shows an actual example in which a 22 kDa surface protein was used to confer protection against subsequent bacterial challenge with Neisseria. See, Specification, Page 53, Table 4. Three other species of the surface protein are disclosed in the specification which are highly structurally similar to the polypeptide used in the example. Consequently, there is no reason to doubt that they

would have the same properties. In fact, this is consistent with the Patent Office's own conclusion in similar examples in the *Written Description Guidelines* (e.g., Page 36, last paragraph).

The boilerplate reasons given in the specification are inadequate to provide any reasonable basis to doubt, let alone reject, the claim are not being enabled. For example, in making the rejection, the Patent Office (Office action, Page 7) quoted from a source that it alleged was authoritative on the subject: "The key problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies and thus protect the host against attack by the pathogen." Indeed, applicant has accomplished exactly that: identification of a surface polypeptide which is established in both *in vitro* and *in vivo* models to possess bacteriolytic activity against Neisseria, and protect against a lethal challenge with the bacteria. See, e.g., Specification, Page 53. Furthermore, specific antigenic epitopes are identified. See, e.g., Specification, Page 60, line 15-Page 61, line 12.

Relevant case law (e.g., described in M.P.E.P. 2164.08) where enablement was found deficient was where actual failures within the scope of the claim were identified, and applicant was claiming entire huge classes (e.g., In Wright: "<u>any and all</u> live, non-pathogenic vaccines, and processes for making such vaccines, which elicit immunoprotective activity in <u>any</u> animal toward any RNA virus." (original emphasis); In Goodman: "The specification did not enable the broad scope of the claims for producing mammalian peptides in plant cells because the specification contained only an example of producing gamma-interferon in a dicot species, and there was evidence that extensive experimentation would have been required for encoding mammalian peptide into a monocot plant at the time of filing"). These defects have not been identified here.

<u>Rejection under §112, second paragraph</u>

The rejection of claim 12 as being indefinite because of its recitation of "stringent conditions" is traversed. Claims are not interpreted in a vacuum, and a skilled worker, upon reading the specification would understand the scope of the claims. In fact, the

Patent Office's *Written Description Guidelines* provide exemplary claims and disclosure which are similar to those at issue here. On page 35-36 of the *Guideline:*

> **Specification**
>
> The specification includes an example wherein the complement of SEQ ID NO:1 was used under highly stringent hybridization conditions (6XSSC and 65 degrees Celsius) for the isolation of nucleic acids that encode proteins that bind to dopamine receptor and stimulate adenylate cyclase activity.
>
> **Claim**
>
> An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1,.
>
> **Analysis**
>
> The art indicates that hybridization techniques using a known DNA as a probe under highly stringent conditions were conventional in the art at the time of filing.

Thus, the specification and claims are clearly in conformance with the *Guidelines* proffered by the Patent Office. Accordingly, there is no basis to maintain the rejection, and it should be withdrawn.

Rejection under §102(a) as anticipated by Merks

In order to anticipate a claim, a prior art reference must be enabling. According to M.P.E.P. 2121.01:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'... ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention.

Merks describe obtaining over 800 hybridoma clones (Page 13, lines 4-5), only one of these which produces an antibody which recognizes a cell surface protein alleged in the Office action to anticipate certain pending claims. The hybridoma was allegedly deposited with the ATCC (Page 19, Claim 8), but a search of the ATCC database shows that it is not publicly available. See, Exhibit A. Without the antibody produced by the hybridoma, Merks does not provide adequate guidance or information to identify the surface antigen, let alone isolate it. Consequently, the reference does not contain an enabling disclosure, and therefore does not anticipate the claimed invention.

It is also urged that Merks does not describe "An isolated polypeptide ... free of any other Neisseria meningitidis polypeptide." Compare, Claims 187-196. The "20 kD" polypeptide of Merks is present in crude extract. See, e.g., Merks, Page 6, line 15-Page 7, line 6. Moreover, Merks provide no information on how to isolate it, especially to make it free of any other Neisseria meningitidis polypeptide. For example, they do not provide the gene, so it could not be produced recombinantly. Compare, in contrast, Applicant's disclosure of recombinant methods. See, e.g., Specification, Page 61, Examples 10-11; Claims 193-194.

Rejection under §102(b) as anticipated by Bhattacharjee et al.

The protein allegedly disclosed in Bhattacharjee et al. is not described as being "resistant to proteinase K" or having "an apparent molecular weight of 22 kDa." It therefore does not meet all the elements of the claim, and can not be anticipatory.

The rejection was maintained because it was stated that the protein described by Bhattacharjee inherently possesses the characteristics recited in the claims. To rebut the inherency, Applicants provided three lines of evidence that the proteins are not the same: (1) a declaration in the parent application by Dr. Bernard Brodeur which distinguishes the two proteins on the basis of their Coomassie blue staining property; (2) molecular weight; and (3) amino acid content. These features do not have to be recited in the claims since the claims already list aspects that are not disclosed in the prior art. The issue is whether the prior art protein is identical to the claimed protein, and thus would inherently possess these recited aspects. Sufficient information has been provided that establishes the non-

identity between the two proteins. The examiner has not rebutted this. Therefore, the rejection should be withdrawn.

Moreover, the claims have now been amended to expressly recites features that are absent in the cited reference. For example, on Page 775, first column, of Bhattacharjee et al., it is stated: "Staining with Coomassie brilliant blue failed to show any protein bands." (See, also Page 776 in the "Discussion."). In contrast, the claimed polypeptides can be stained with Coomassie blue. See, e.g., Page 6, line 24-Page 9, line 22, Example 1 on Page 28, lines 13-29, Page 42, line 16-Page 43, line 35

In view of the above remarks and amendments, favorable consideration of the application is courteously requested. If there is any remaining issue(s) which can be expeditiously resolved by a telephone conference, the Examiner is courteously requested to telephone the undersigned at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to the Deposit Account No. 13-3402.

Respectfully submitted,

Richard M. Lebovitz, No. 37,067

Millen, White, Zelano & Branigan, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Blvd., Suite 1400
Arlington, Virginia 22201
direct dial: (703) 812-5317
email: lebovitz@mwzb.com

Attorney Docket No.: PHARMA-147C1

Date Filed: August 3, 2004